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An efficient palladium–benzimidazolyl phosphine complex for the Suzuki–Miyaura coupling of aryl mesylates: facile ligand synthesis and metal complex characterization†

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A new class of easily accessible hemilabile benzimidazolyl phosphine ligands has been developed. The ligand skeleton is prepared from commercially available and inexpensive *o*-phenylenediamine and 2-bromobenzoic acid. With catalyst loading down to 0.5 mol% palladium, excellent catalytic activity towards the Suzuki–Miyaura coupling of aryl mesylates is still observed. This represents the lowest catalyst loading achieved so far for this reaction in general. X-Ray crystallography shows that new ligand L2 is coordinated with Pd in a κ^2-P,N fashion.

Palladium-catalyzed Suzuki–Miyaura coupling of aryl halides and arylboronic acids is one of the most versatile tools for the synthesis of diversified biaryls which have numerous applications in pharmaceutical, natural product, advanced material and agricultural chemistry.[1,2] Huge efforts have been undertaken by researchers aiming to activate and utilize aryl halides, especially chlorides, as electrophiles for a variety of cross-coupling reactions.[1,3] In fact, aryl sulfonates are important alternatives and/or complements to aryl halides in cross-coupling reactions since their availability and substitution pattern on the aromatic ring may have differences when compared to aryl halides.[4] However, previous coupling reactions were mainly focused on more reactive aryl triflates due to lack of effective catalysts for activating aryl tosylates and mesylates. Indeed, aryl tosylates and mesylates are ideal phenolic electrophiles as they are also easily accessible from phenols, yet in relatively low cost.[5] They have a better hydrolytic stability when compared to the corresponding aryl triflates. Moreover, aryl mesylates offer a more attractive atom-economy than aryl tosylates.[6] Although beneficial features are noted, aryl mesylates are challenging substrates as they are even less reactive than the corresponding aryl tosylates in cross-coupling reactions.[7]

Pioneering establishments in designing effective phosphines for Pd-catalyzed coupling of aryl halides generally contain electron-rich (to enhance oxidative addition) and sterically bulky (to facilitate reductive elimination) components. However, well-known efficient ligands such as P(*t*-Bu)$_3$, PCy$_3$, and JohnPhos in palladium-catalyzed cross-coupling of aryl halides are obscurely ineffective ligands in the case of aryl sulfonates (Fig. 1).[8]

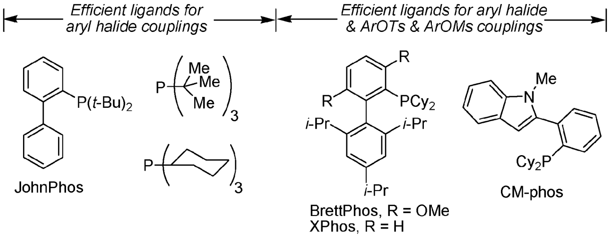

Fig. 1 Selected ligand examples for efficient Suzuki coupling of aryl halides, tosylates and mesylates.

Recently, we reported a palladium catalyst system (Pd–CM-phos) for the cross-coupling of aryl mesylates and arylboronic acids.[9] Buchwald's BrettPhos also displayed excellent reactivity in palladium-catalyzed Suzuki–Miyaura coupling of both aryl tosylates and mesylates.[10]

With respect to the established catalytic systems for promoting Suzuki coupling of aryl halides, catalysts developed for Suzuki coupling of challenging sulfonates, such as aryl tosylates[11] and mesylates,[12] are still limited. In fact, there is no literature report concerning the successful application of P,N-type ligands for this reaction. Thus, versatile catalysts for widespread applications of aryl sulfonate coupling reactions are needed. Certainly, it would be further attractive if structurally diversified ligand skeletons can be assembled from multiple components *via* a simple "cross-matching" synthetic strategy.

Phosphine ligands containing potential hemilabile coordinating groups for cross-coupling reactions have been studied in the past decade (Fig. 2).[13] Hor and co-workers described the dynamic interaction between the hemilabile group (*e.g.* nitrogen donor) and the palladium center that could increase the catalyst longevity.[13b]

Inspired by the unique feature of P,N-type hemilabile ligands in cross coupling of aryl halides and the effectiveness of monophosphines (*e.g.* Brettphos and CM-phos) for the coupling of aryl mesylates, we are interested in designing a new family of hemilabile P,N-type ligands for promoting aryl

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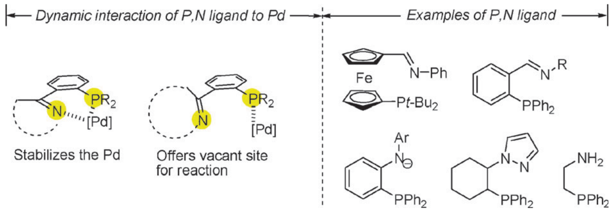


Fig. 2 Interactions and examples of hemilabile P,N ligands for Suzuki coupling of aryl halides.

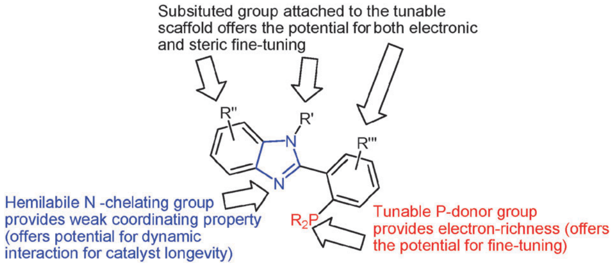
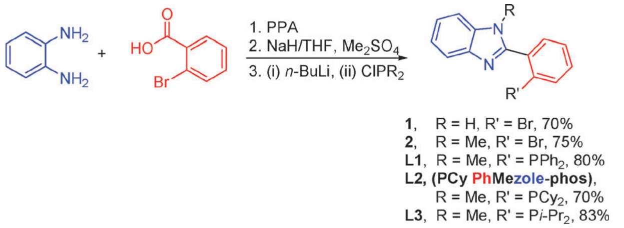


Fig. 3 Features of new P,N-type phosphine ligand family.

mesylate coupling that can have a better catalyst longevity (Fig. 2). To the best of our knowledge, there has been no successful example reported to date for P,N ligands in C–C bond coupling using aryl mesylates. Herein, we report our efforts on developing a new class of hemilabile benzimidazolyl phosphines for the Suzuki coupling of aryl mesylates. This new series of ligands embodies a highly tunable, yet easily accessible, main skeleton with a hemilabile coordinating site (Fig. 3). The ligand backbone could be obtained by a direct assembly of commercially available and inexpensive *o*-phenylenediamine and 2-bromobenzoic acid in the presence of polyphosphoric acid (Scheme 1).[14]

This synthetic protocol could generate multiple entities of ligand structures *via* a "cross-matching" approach from two components. Particularly noteworthy is that the ligand scaffold, 2-(2-bromophenyl)-1*H*-benzoimidazole (**1**), could be synthesized in a 100 mmol scale with good yield without difficulties in both synthetic and purification processes. With the methylated ligand precursor **2**, the benzimidazolyl phosphines **L1–L3** could be afforded in good yields by lithiation and subsequently trapping with $ClPR_2$ (Scheme 1). This family of ligands exhibits excellent air stability in both solid and solution states. It should be noted that no chromatographic purification is needed in all synthetic steps which offers additional advantage to this new ligand series.

To test the effectiveness of the new ligands, electronically neutral 4-*tert*-butylphenyl mesylate and 4-tolylboronic acid were used as the model substrates in our benchmark reaction (see ESI†, Table S1). A catalyst loading of 0.5 mol% Pd was initially applied for evaluating the new ligand efficacy. Ligand **L1** with a diphenylphosphino moiety provided trace substrate conversion while the dicyclohexylphosphino analogue, **L2**, gave the best catalytic activity. Ligand **L3** bearing a diisopropylphosphino moiety showed a lower catalytic activity towards the Suzuki coupling reaction. Interestingly, the P,N ligand **L2** displayed a significantly better activity than CM-phos in cross-coupling of aryl mesylates. Upon investigating the metal/ligand ratio from 1 : 1 to 1 : 4, the ratio of 1 : 2 provided the highest yield, which differs from the Pd–CM-phos system in which the metal/ligand ratio was at least 1 : 4 for giving the best result.[9b]



Scheme 1 Synthetic pathway of the benzimidazolyl phosphine ligands.

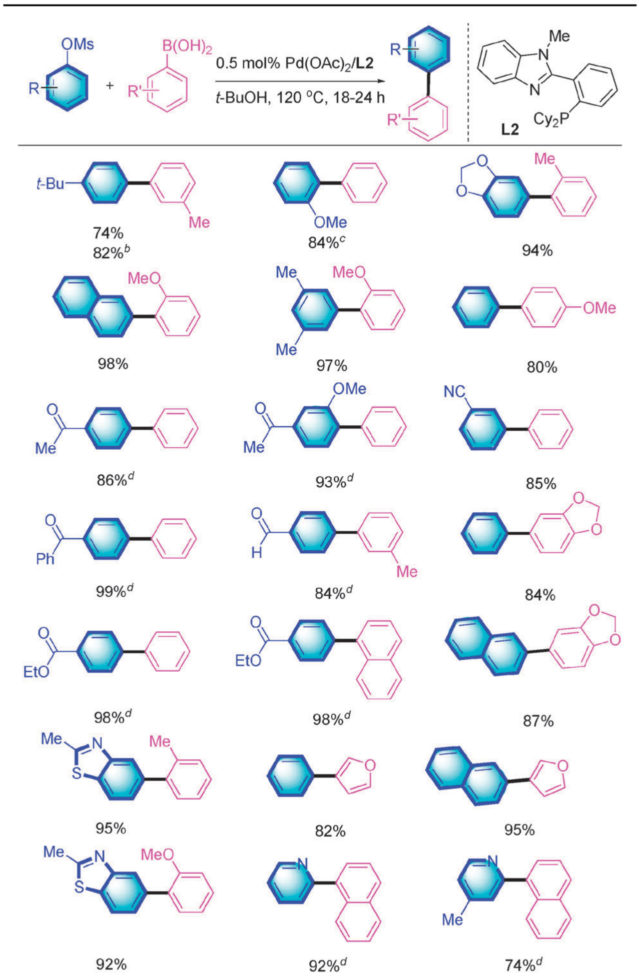
The hemilabile group possibly reduces the need for ligand concentration to maintain the catalyst activity. Thus $Pd(OAc)_2$ and metal/ligand ratio 1 : 2 were then chosen for further screening. For the palladium sources, $Pd_2(dba)_3$, $PdCl_2$, $Pd(TFA)_2$, gave similar yields while $Pd(OAc)_2$ provided the best result. Several bases were tested in the presence of ligand **L2**. Although K_3PO_4 was the most efficient base among several bases investigated, some phenolic side products (from hydrolysis of sulfonate) were found after prolonged heating. K_2CO_3 and Na_2CO_3 showed a lower reactivity for the aryl mesylate coupling reaction. Yet, no phenolic side product was observed after 24 h heating.

The scope of this reaction was then investigated under the preliminary optimized conditions. A range of aryl mesylates were examined and the results are listed in Table 1. In general, 0.5 mol% of Pd was effective to handle a wide range of aryl mesylates and complete conversions were observed within 24 hours. The deactivated aryl mesylate containing an *ortho*-methoxy substituted group was found to be a feasible coupling partner. Either *ortho*-substituted aryl mesylates or arylboronic acids were also good substrates for this reaction. The functionalized aryl mesylates containing keto, ester, aldehyde and nitrile groups were found to be feasible electrophiles under the reaction conditions. Phenolic side products were minimized by using Na_2CO_3 as base for some substrates, isolated yields of desired products could be as high as 99%. Apart from common aryl mesylates, heteroaryl mesylates were also examined. Benzothiazolyl and pyridyl substrates could couple with arylboronic acids to furnish products in moderate to excellent yields. It is worthy of note that heteroaryl boronic acid was found to be a capable coupling partner in this reaction.

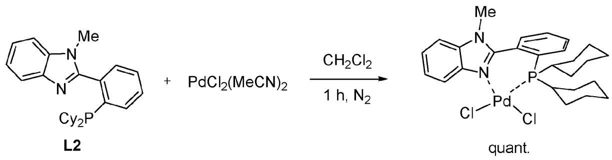
To further gain the insight into the metal–ligand interactions, we attempted to complex the $PdCl_2(CH_3CN)_2$ with one equivalent of **L2** in dichloromethane at room temperature (Scheme 2). The X-ray crystallographic data confirmed that the benzimidazolyl ligand **L2** is coordinated in a κ^2-P,N fashion (see ESI† for details).

In summary, a new series of P,N hemilabile ligands has been developed. This family of ligands embodies a benzimidazolyl backbone and is easily accessible from commercially available and inexpensive diamine and benzoic acid.[14] The degree of potential structural variation is high, since this protocol can generate multiple entities of skeletons from two main components. Particularly noteworthy is that all ligand synthetic steps require no chromatographic purification which potentially gives a feature of scale up synthesis. To the best of our knowledge, we have succeeded in showing the first examples of P,N ligands that can effectively deal with aryl mesylate coupling. Moreover, we have also achieved the lowest catalyst

Table 1 Palladium-catalyzed Suzuki coupling of aryl mesylates[a]



[a] Reaction conditions: $Pd(OAc)_2$ (0.5 mol%), Pd : **L2** = 1 : 2, ArOMs (1.0 mmol), arylboronic acid (2.0 mmol), K_3PO_4 (3.0 mmol), *t*-BuOH (3 mL), at 120 °C under N_2 for 24 h. Isolated yields were reported. [b] 1 mol% of $Pd(OAc)_2$. [c] K_2CO_3 as base. [d] Na_2CO_3 as base, at 120 °C under N_2 for 18 h.



Scheme 2 Complexation of P,N ligand **L2** with $PdCl_2(MeCN)_2$.

loading reported so far for Suzuki coupling of aryl mesylates in general. This catalyst longevity finding possibly provides relevance for a direction of future ligand design for conducting other difficult aryl mesylate couplings.

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